PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#12 JRP 2/1/02

Applicant	:	John A. Arcadi
Application No.	:	09/383,114
Filed	:	August 25, 1999
Title	:	COMPOSITION AND METHOD FOR TREATING CARCINOMA (as amended)
Grp./Div.	:	1614
Examiner	:	J. Goldberg
Docket No.	:	35687/RWJ/H29

DECLARATION

Assistant Commissioner for Patents
Washington, D.C. 20231

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Pasadena, CA 91109-7068

Commissioner:

I, Lawrence W. Jones, declare that:

1. I am a licensed physician in the State of California, and the Director of Prostate Research Program at Huntington Medical Research Institutes (HMRI), a non-profit medical research organization and the assignee of the above patent application. I have been working in the field of treating prostate cancer for more than 28 years, and have worked as an unpaid volunteer for HMRI since 1974. I am thoroughly familiar with the patent application, and I have no financial interest in it.

2. The patent application covers the use of rhodamine-123 for treating hormone-refractory prostate cancer, which kills 40,000 men annually in the United States. Before this invention, there was no known life-prolonging treatment for this disease.

3. I am also familiar with the Office actions dated 10/23/00 and 07/13/01, which reject claims 1-27 in this application as unpatentable over the two Arcadi references of 1986 and 1990.

4. HMRI filed with the U.S. Food and Drug Administration (FDA) an Investigational New Drug Phase I Application, which was approved for the experimental testing of rhodamine-123 to treat human prostate cancer *in vivo*. Clinical testing to determine a safe dosage level of rhodamine-123 for humans began under my supervision as Principal Investigator on February 1, 1999. Under Phase I of

the approved protocol, 27 volunteer patients are to be treated in nine groups of three each, with each volunteer receiving a single dose of rhodamine-123.

5. As stated in my previous Declaration dated 2/23/2001 in this application, clinical testing done under my direction showed a substantial decrease in prostate specific antigen (PSA) for 4 out of 12 patients undergoing clinical tests under my supervision. For 2 of those patients, the decrease in PSA exceeded 50%, which is strong evidence that median survival time for such patients may be significantly extended.

6. Over the past 50 years, hundreds of drugs tested *in vitro* and in laboratory animals have shown potential as antitumor agents, but subsequently failed in clinical tests, or never reached that stage. For example, see U.S. Patent 5,360,803 (filed November 6, 1992, and assigned to Dan Farber Cancer Institute and Fuji Photo Film Co., Ltd.), which discloses at least 348 antitumor agents for treating prostate cancer in humans. I review regularly publications and reports dealing with agents for treating cancer, and as far as I am aware, none of those disclosed by that patent have been accepted by the medical profession as a treatment for prolonging life of patients afflicted with hormone-refractory prostate cancer.

7. Contrary to the statement in the 07/13/01 Office action on page 2, Dr. Arcadi's 1986 and 1990 articles would not cause one of ordinary skill in this work to reasonably expect that rhodamine-123 would be any more effective in combating human prostate carcinoma than any of many other drugs which have been tested *in vitro* and in laboratory animals with promising results, but which have failed to produce any therapeutic effects in human patients. Nothing in either of Dr. Arcadi's articles discloses that life can be prolonged by treating victims of prostate cancer with rhodamine-123.

8. An important problem in the management of prostate cancer is the heterogeneity of the disease. Unequivocal evidence from animal studies, from the growth of human prostate cancer in tissue culture, in the xenograft system, and from human biopsy material shows that many different types of tumor cells exist within prostate cancer. Accordingly, even though a drug may be demonstrated to be effective in laboratory *in vitro* and animal experiments, that does not justify a "reasonable expectation" that it will be effective in treating human prostate cancer. This is well recognized by skilled workers in this field. For example, attached to this Declaration as Exhibit A is a paper by the inventor and others (including me) entitled "Studies of Rhodamine-123: Effect on Rat Prostate Cancer and Human Prostate

Cancer Cells In Vitro," presented in the *Journal of Surgical Oncology* 59:86-93 (1995), which describes some experimental work providing some basis for this patent application. Under "Editorial Comments" at the end of the paper, Dr. T. Vincent Shankey, with the Departments of Urology and Pathology at Loyola University Medical Center in Maywood, Illinois, rejects the work described in the paper as supporting "the thesis that Rh-123 may be an effective agent for the treatment of metastatic hormone-refractory prostate cancer" because it "is a connection that has too often failed in the past." Dr. Shankey's criticism cites other authorities who have pointed out that "the local environment of solid malignancies *in situ* has a profound impact on the responsiveness or nonresponsiveness of cancers where they really count to a patient in his or her body."

9. Further evidence of skepticism about rhodamine-123 long after Dr. Arcadi's 1986 and 1990 articles appear in an article entitled "Synthesis and Evaluation of Novel Rhodacyanine Dyes That Exhibit Anti-Tumor Activity" by Kawakami et al., published in the *Journal of Medical Chemistry* in 1997 at 40, 3151-3160 (copy attached as Exhibit B). On page 1 of that article, the authors, referring to various organic compounds, including rhodamine-123, which have been explored as potential antitumor drugs, state that: "In spite of high potential as antitumor agents, none of them have met the criteria for clinical development, such as water solubility, stability, toxicity, and pharmacokinetics".

10. At least as early as 1982, rhodamine-123 was known to reduce the clonal growth of carcinoma cells *in vitro*. For example, see attached Exhibit C, an article entitled "Rhodamine-123 Selectively Reduces Clonal Growth of Carcinoma Cells *In Vitro*", published in *Science*, Vol. 218, pp. 1117 & 1118, (10 December 1982). Dr. Arcadi's work was published in 1986 and 1990. Even so, there was still substantial professional skepticism about the efficacy of rhodamine-123 for treating human prostate cancer. For example, as late as 1997 (see Exhibit B referred to above in paragraph 9), workers at Fuji Photo Film Co., Ltd. and Harvard Medical School dismissed rhodamine-123 as failing to meet the necessary criteria for clinical development.

11. Based on my experience and the skepticism of colleagues with respect to the possible efficacy of rhodamine-123 for treating prostate cancer, the work published by Dr. Arcadi in 1986 and 1990 does not provide a reasonable expectation that rhodamine-123 would be any more effective for combating human prostate cancer than any of many other agents which showed promising laboratory results, and failed to be therapeutic. The drug industry and the medical profession have spent millions of dollars and thousands of research hours seeking an effective therapy for prostate cancer. By any

objective standard, if Dr. Arcadi's 1986 and 1990 articles had actually created a reasonable expectation that treatment with rhodamine-123 would prolong the life of prostate cancer victims, the compound would have been put to wide use instead of being dismissed as clinically inadequate by other workers in that field.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 10/30/01

By _____
Lawrence W. Jones, M.D.

RWJ/mas
Attachments: Exhibits A-C
CLS PAS390616.1-*-10/30/01 10:37 AM